microns by 10-150 microns with a depth from about 0.5-5 microns.

40. (amended) A composition comprising the crystals of Claim 33.

~~42. The composition of Claim 40 wherein the composition~~ additionally comprises zinc.

~~75. (new) A composition comprising the crystals of Claim 39.~~

76. (new) The composition of Claim 75 wherein the composition additionally comprises zinc.

Remarks

Applicants submit that the amended claim set presented above is fully supported by the specification and presents no new matter. The claims have support throughout the specification as originally filed. For example:

Claim 33:

Claim 33 has been amended to replace Val-8-GLP-1(7-37)OH with SEQ ID NO:5 which is the SEQ ID NO: that corresponds to Val-8-GLP-1(7-37)OH in the Specification. The sequence of Val-8-GLP-1(7-37)OH was provided in the Specification as originally filed. The sequence of GLP-1(7-37)OH is provided on page 5, line 9 and labeled SEQ ID NO:1. Val-8-GLP-1(7-37)OH is listed on page 5, line 19. The nomenclature is described on page 4, line 31 through p. 5, line 5. The amino terminus is assigned residue 7. Thus, Val-8-GLP-1(7-37)OH is GLP-1(7-37)OH [SEQ ID NO:1] wherein valine is substituted for the wild-type residue at position 8. Furthermore, SEQ ID NO:2 provides a formula for GLP-1 analogs that includes Val-8-GLP-1(7-37)OH [see p. 5, line 25]. The X at position 8 can be Val as well as various other residues. Finally, Example 1 describes the Val-8 species used as "chemically synthesized

GLP-1(7-37)OH analog having Val substituted for Ala in position 8 (V8-GLP-1)." See p. 16, line 3.

Claim 33 has also been amended to include dimension limitations for the crystals. On page 10, line 1 the Specification provides "The flat rod shaped or plate-like GLP crystals of the present invention, which are prepared using the claimed process, vary in size and shape to some degree. Generally, they range in size from approximately 2-25 microns (μm) by 10-150 μm and are flat, having a depth of approximately 0.5 to 5 μm." In addition, a number of examples describe the crystals produced in terms of dimension. Example 9 describes the crystals as "40 microns long, 15 microns wide, and 3 microns thick." [p. 22, line 20]. Example 10 described the crystals as "10 to 30 microns long and 10 microns wide." [p. 23, line 22]. Example 13 describes the crystals as "150 μm in length, approximately 25 μm wide and less than 5 μm thick." [p. 25, line 8]. OK

Claim 33 also specifies that the crystallization solution is an aqueous solution as described in the Examples.

Claims 34 through 38 and 40:

These claims either directly or indirectly depend from Claim 33. The amendments merely use the term peptide which is defined in independent claim 33 to be SEQ ID NO:5 (Val-8-GLP-1(7-37)OH.

The concentration ranges of peptide, the pH ranges, the ethanol ranges, the zinc concentration and the ammonium sulfate concentration have basis in the original claims as filed as well as throughout the rest of the Specification.

For example, original process claim 2 provides a peptide concentration of between 1-10 mg/mL and a pH range between 6 and 7. Original process Claim 3 provides zinc in a molar ratio between 0.5 and 1.7 to peptide and a peptide concentration between 1-20 mg/mL as well as a pH range between 7-10. Additional support in the Specification can be found on pages 11-13. The alcohol concentration is stated as ranging from 2-15% (v/v), preferable 3-13%. Ammonium sulfate

concentration is provided as approximately 1% (w/v). [p. 11, lines 19-26]. Peptide concentration ranges of 1-20 mg/mL, preferably 2-10 mg/mL are provided and the total zinc as a molar ratio to peptide is provided as 0.5 to 1.7, preferably 0.6 to 1.5 [p. 12, lines 10-17]. The optimal pH ranges are provided as pH 6-7, preferably 6.4 +/- 0.2 (p. 11, lines 15-16) and as pH 7-10, preferably about 7.2 - 9.7 (p. 12, lines 12-13).

Claims 39 and 75-76:

These claims are directed to crystals made using a monosaccharide or disaccharide instead of an alcohol as specified in Claim 33.

Originally filed process Claim 2 and 3 were directed towards making crystals using either an alcohol or a mono or disaccharide. Pending Claim 33 was amended to exclude mono and disaccharides and instead crystals made using these components are encompassed by independent Claim 39.

There is clear support for the use of a genus of monosaccharides and disaccharides to make the crystals of the present invention. There are two specific examples describing in detail crystals made using a monosaccharide and a disaccharide (see also Applicants response to the Examiner's final rejection pages 4 through 7).

On page 3, line 18 of the Specification the inventors state that "tetragonal flat rod shaped or plate-like crystals . . . could be reproducibly formed from a mother liquor containing a GLP dissolved in a buffered solution and . . . a mono or disaccharide, over a wide range of pH conditions." On page 12, line 3, the Specification provides that "mono or disaccharides may be substituted for the alcohol in the same ratios on a weight to volume basis." A list of mono and disaccharides suitable for use in making the crystals of the present invention is also provided.

Finally, there are two specific examples wherein Val-8-GLP-1 crystals are made using a monosacchardie or disaccharide. Example 9 on page 22 provides a protocol to

make crystals with 5% trehalose (a disaccharide). On line 18, the inventors state that "[a]fter 24 hours V8-GLP-1 crystal clusters and single rectangular crystals were identified." Measurements of these crystals are also provided. Example 10 on page 23 provides a protocol to make crystals with 10% mannitol (a monosaccharide). Measurements of these crystals are also provided.

Claims 75 and 76 are composition claims and comprise the crystals of claim 39 as well as the addition of zinc to those compositions. On page 4, line 1 the Specification provides: "The crystal compositions of the present invention are pharmaceutically attractive because they are relatively uniform and remain in suspension for a longer period of time than the crystalline clusters or amorphous crystalline suspensions . . . . Most importantly, the crystal compositions of the present invention display extended, uniform, and reproducible pharmacokinetics which can be modulated by adding zinc using conventional crystal soaking techniques or, alternatively, by including zinc in the crystallization solution." Additional support can be found on p. 13, line 15 wherein it is stated: "the invention provides homogenous compositions of individual tetragonal flat rod shaped or plate-like crystal of GLP's. Prior to the processes herein disclosed and claimed, such compositions could not be achieved." Additional support for the addition of zinc is also provided on p. 13, line 24.

Respectfully submitted,

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Attachment A

Marked-up copy of amendments as required by 37 C.F.R. § 1.121(b)(1)(iii)

Replacement paragraph beginning p. 5, line 12:

"GLP-1 analog" is defined as a molecule having one or more amino acid substitutions, deletions, inversions, or additions relative to GLP-1(7-37) and may include the d-amino acid forms. Numerous GLP-1 analogs are known in the art and include, but are not limited to, GLP-1(7-34) (SEQ ID NO:8), GLP-1(7-35) (SEQ ID NO:9), GLP-1(7-36)NH_2 (SEQ ID NO:10), Gln^9-GLP-1(7-37) (SEQ ID NO: 11), [d]D-Gln^9-GLP-1(7-37) (SEQ ID NO:12), Thr^{16}-Lys^{18}-GLP-1(7-37) (SEQ ID NO:13), and Lys^{18}-GLP-1(7-37) (SEQ ID NO:14), Gly^8-GLP-1(7-36)NH_2 (SEQ ID NO:15), Gly^8-GLP-1(7-37)OH (SEQ ID NO: 16), Val^8-GLP-1(7-37)OH (SEQ ID NO:5), Met^8-GLP-1(7-37)OH (SEQ ID NO:18), acetyl-Lys^9-GLP-1(7-37) (SEQ ID NO:19), Thr^9-GLP-1(7-37) (SEQ ID NO:20), D-Thr^9-GLP-1(7-37) (SEQ ID NO:21), Asn^9-GLP-1(7-37) (SEQ ID NO:22), D-Asn^9-GLP-1(7-37) (SEQ ID NO:23), Ser^{22}-Arg^{23}-Arg^{24}-Gln^{26}-GLP-1(7-37) (SEQ ID NO:24), Arg^{23}-GLP-1(7-37) (SEQ ID NO:25), Arg^{24}-GLP-1(7-37) (SEQ ID NO:26), α-methyl-Ala^8-GLP-1(7-36)NH_2 (SEQ ID NO:27), and Gly^8-Gln^{21}-GLP-1(7-37)OH (SEQ ID NO:28), and the like.

Attachment B

Marked-up copy of amendments as required by 37 C.F.R. § 1.121(b)(1)(iii)

Marked-up Claim amendments:

33. (amended) Flat rod shaped or plate-like crystals of [valine-8-glucagon-like peptide-1 (7-37)OH [Val-8-GLP-1(7-37)OH]] a peptide having the amino acid sequence of SEQ ID NO:5 prepared by crystallizing [Val-8-GLP-1(7-37)OH] the peptide from [a] an aqueous solution comprising [Val-8-GLP-1(7-37)OH] the peptide and between about 2-15% (v/v) ethanol or between about 2-15% (v/v) propanol [or a monosaccharide or a disaccharide], and wherein the solution optionally comprises ammonium sulfate or zinc and provided that the crystals vary in size from between about 2-25 microns by 10-150 microns with a depth from about 05-5 microns.

34. (amended) The [Val-8-GLP-1] crystals of Claim 33 wherein the concentration of [Val-8-GLP-1(7-37)OH] the peptide in the solution is between about 1-10 mg/ml and the pH of the solution is between about 6 and 7.

35. (amended) The [Val-8-GLP-1] crystals of Claim 34 wherein the concentration of [Val-8-GLP-1(7-37)OH] peptide in the solution is between about 2-7 mg/ml and the solution comprises between about 3-13% ethanol (v/v).

36. (amended) The [Val-8-GLP-1] crystals of Claim 35 wherein the solution comprises ammonium sulfate at a concentration of about 1% (w/v).

37. (amended) The [Val-8-GLP-1] crystals of Claim [34] 33 wherein the concentration of [Val-8-GLP-1(7-37)OH] peptide in the solution is between about 1-20 mg/mL, the molar ratio of zinc to [Val-8-GLP-1(7-37)OH] peptide is between about 0.5 to 1.7, and the pH of the solution is between

about 7-10.

38. (amended) The [Val-8-GLP-1] crystals of Claim 37 wherein the concentration of [Val-8-GLP-1(7-37)] peptide in the solution is between about 2-10 mg/mL, the molar ratio of zinc to [Val-8-GLP-1(7-37)OH] peptide is between about 0.6 to 1.5, and the pH of the solution is between about 7.2-9.7.

39. (amended) [The Val-8-GLP-1] Flat rod shaped or plate-like crystals [of Claim 33] of a peptide having the amino acid sequence of SEQ ID NO:5 prepared by crystallizing the peptide from an aqueous solution comprising the peptide and between about 2-15% (w/v) [wherein the solution comprises] of a mono or disaccharide selected from trehalose, mannitol, glucose, erythrose, ribose, galactose, fructose, maltose, sucrose or lactose; and wherein the solution optionally comprises ammonium sulfate or zinc and provided that the crystals vary in size from between about 2-25 microns by 10-150 microns with a depth from about 0.5-5 microns.

40. (amended) A composition comprising [individual flat rod shaped or plate-like] the crystals of [Val-8-GLP(7-37)OH] Claim 33.

42. The composition of Claim 40 wherein the composition additionally comprises zinc.